United Research Laboratories, Inc.
Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street
Philadelphia, PA 19124

215-288-6500
www.urlmutual.com



February 4, 2004

Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

## Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, on behalf of Mutual Pharmaceutical Company in accordance with Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.93 to request that the Commissioner of Food and Drugs permit the filing of an Abbreviated New Drug Application (ANDA) for a drug that has the same active ingredient, route of administration, and dosage strengths as a drug listed in FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluation" (i.e., the Orange Book), but differs in dosage form.

### A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration make a determination that the drug product, Doxycycline Hyclate Capsules, 75mg and 100 mg, is suitable for evaluation under an ANDA. The referenced product is Doryx® Capsules, 75 mg and 100 mg (NDA 50-582). This Petition requests a change in dosage from that listed in the Orange Book as "capsule, coated pellets, oral" to an oral capsule containing powder or other fill that is different than coated pellets.

### B. Statement of Grounds

The Federal Food, Drug and Cosmetic Act provides for the submission of an ANDA for a drug product that differs in dosage form from that of the listed drug provided the FDA has approved a petition that proposed filing such an application. A copy of the most recent on-line listing of the electronic "Approved Drug Products with Therapeutic Equivalence Evaluations", included as Attachment 1, lists the reference drug, Doryx® Capsules, by Mayne Pharma USA. That listing further specifies that the dosage form of the reference drug is "capsule, coated pellets, oral".

The proposed drug product is an oral capsule dosage form, as is the reference listed drug (RLD), and is in the same dosage strengths as the RLD. The difference between the proposed drug product and the RLD, which is the subject of this petition, is that the proposed drug product will contain a powder or other material that is not comprised of coated pellets. The proposed product contains the same active ingredient as the RLD and is intended for the same route of administration. Thus, the proposed product will be labeled with the same dosage recommendations as the RLD and is expected to have the same therapeutic effect when used as indicated in the approved labeling.

In addition, the labeling for the proposed product is expected to be substantially the same as the RLD with the exception of changes necessitated by the fact that the product is manufactured by a different company, the product does not contain coated pellets, the product is referred to by the generic name Doxycycline Hyclate Capsules rather than the Doryx® brand name, and the product's appearance and "How Supplied" information are different. The initial draft labeling and the approved labeling for the RLD are included as Attachments 2 and 3, respectively.

2004P-0054



CP1

C. **Environmental Impact**

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. **Economic Impact**

Pursuant to 21 CFR 10.30(b), the economic impact information will be submitted if requested by the Agency.

E. **Certification**

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,

Robert Dettery
Vice President, Regulatory Affairs
Mutual Pharmaceutical Company
1100 Orthodox Street
Philadelphia, PA 19124
(215) 288-6500

Attachments:
1) electronic Orange Book listing
2) draft labeling
3) Doryx® Capsules labeling

Cc: G. Davis (Office of Generic Drugs)

# ATTACHMENT 1

**Search results from the "Rx" table for query on "050582."**

| | |
|---|---|
| Active Ingredient: | DOXYCYCLINE HYCLATE |
| Dosage Form;Route: | Capsule, Coated Pellets; Oral |
| Proprietary Name | DORYX |
| Applicant: | MAYNE PHARMA USA |
| Strength: | EQ 100MG BASE |
| Application Number: | 050582 |
| Product Number: | 001 |
| Approval Date: | JUL 22, 1985 |
| Reference Listed Drug: | Yes |
| RX/OTC/DISCN: | RX |
| TE Code: | AB |
| Patent and Exclusivity Info for this product: | Click Here |

| | |
|---|---|
| Active Ingredient: | DOXYCYCLINE HYCLATE |
| Dosage Form;Route: | Capsule, Coated Pellets; Oral |
| Proprietary Name | DORYX |
| Applicant: | MAYNE PHARMA USA |
| Strength: | EQ 75MG BASE |
| Application Number: | 050582 |
| Product Number: | 002 |
| Approval Date: | AUG 13, 2001 |
| Reference Listed Drug: | No |
| RX/OTC/DISCN: | RX |
| TE Code: | |
| Patent and Exclusivity Info for this product: | Click Here |

Thank you for searching the **Electronic Orange Book**

Return to Electronic Orange Book Home Page

Rx Only

## DOXYCYCLINE HYCLATE CAPSULES USP

### DESCRIPTION

Doxycycline Hyclate Capsules contain doxycycline hyclate for oral administration. Inactive ingredients are croscarmellose sodium, D&C Red #28, FD&C Blue #1, gelatin, magnesium stearate, microcrystalline cellulose, titanium dioxide, and anhydrous lactose.

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline and available as doxycycline hyclate. The chemical designation of this light-yellow crystalline powder is alpha-6-desoxy-5-oxytetracycline. Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

### CLINICAL PHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile and excreted in the urine and feces at high concentrations and in a biologically active form.

Doxycycline is virtually completely absorbed after oral administration. Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/mL of doxycycline at 2 hours decreasing to 1.45 mcg/mL at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 mL/min). This percentage excretion may fall as low as 1–5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min). Studies have shown no significant difference in serum half-life of doxycycline (range 18–22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

Microbiology: Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative organisms. The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is common.

Susceptibility Tests: Diffusion Techniques: The use of antibiotic disc susceptibility test methods which measure zone diameter gives an accurate estimation of susceptibility of organisms to doxycycline hyclate. One such standard procedure[1] has been recommended for use with discs for testing antimicrobials. Doxycycline 30mcg discs should be used for the determination of the susceptibility of organisms to doxycycline.

With this type of procedure, a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue and fluids (e.g., urine) in which high antibiotic levels are obtained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With the doxycycline disc, a zone of 16 mm or greater indicates susceptibility, zone sizes of 12 mm or less indicate resistance, and zone sizes of 13 to 15 mm indicate intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mcg tetracycline disc should give zone diameters between 19 and 28 mm for *S. aureus* ATCC 25923 and between 18 and 25 mm for *E. coli* ATCC 25922. The 30 mcg doxycycline disc should give zone diameters between 28 and 39 mm for *S. aureus* ATCC 25923, and between 18 and 24 mm for *E. coli* ATCC 25922.

Dilution Techniques: A bacterial isolate may be considered susceptible if the MIC (minimal inhibitory concentration) value for doxycycline is less than 4 mcg/mL. Organisms are considered resistant if the MIC is greater than 12.5 mcg/mL. MICs greater than 4.0 mcg/mL and less than 12.5 mcg/mL indicate intermediate susceptibility.

As with standard diffusion methods, dilution procedures require the use of laboratory control mechanisms. Standard doxycycline powder should give MIC values in the range of 0.25 mcg/mL and 1.0 mcg/mL for *S. aureus* ATCC 25923. For *E. coli* ATCC 25922 the MIC range should be between 1.0 mcg/mL and 4.0 mcg/mL.

### INDICATIONS AND USAGE

Doxycycline is indicated in infections caused by the following microorganisms:

Rickettsiae (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers).

*Mycoplasma pneumoniae* (PPLO, Eaton's agent).

Agents of psittacosis and ornithosis.

Agents of lymphogranuloma venereum and granuloma inguinale.

The spirochetal agent of relapsing fever (*Borrelia recurrentis*).

The following gram-negative microorganisms:

*Haemophilus ducreyi* (chancroid)

*Yersinia pestis* (formerly *Pasteurella pestis*)

*Francisella tularensis* (formerly *Pasteurella tularensis*)

*Bartonella bacilliformis*

*Bacteroides* species

*Vibrio cholerae* (formerly *Vibrio comma*)

*Campylobacter fetus* (formerly *Vibrio fetus*)

*Brucella* species (in conjunction with streptomycin)

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:

*Escherichia coli*

*Enterobacter aerogenes* (formerly *Aerobacter aerogenes*)

*Shigella* species

*Mima* species and *Herellea* species

*Haemophilus influenzae* (respiratory infections)

*Klebsiella* species (respiratory and urinary infections)

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriological testing indicates appropriate susceptibility to the drug:

*Streptococcus* species:

Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

*Diplococcus pneumoniae*,

*Staphylococcus aureus* (respiratory, skin and soft-tissue infections). Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to:

*Treponema pallidum* and *Treponema pertenue* (syphilis and yaws)

*Listeria monocytogenes*

*Clostridium* species

*Fusobacterium fusiforme* (Vincent's infection)

*Actinomyces* species

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

In severe acne, doxycycline may be useful adjunctive therapy.

Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis may be treated with oral doxycycline alone, or with a combination of topical agents. Doxycycline is indicated for the treatment of uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis*.[2]

Doxycycline is indicated for the treatment of nongonococcal urethritis caused by *Chlamydia trachomatis* and *Ureaplasma urealyticum* and for the treatment of acute epididymo-orchitis caused by *Chlamydia trachomatis*.[3]

Doxycycline is indicated for the treatment of uncomplicated gonococcal infections in adults (except for anorectal infections in men), the gonococcal arthritis-dermatitis syndrome and acute epididymo-orchitis caused by *N. gonorrhoeae*.[2]

### CONTRAINDICATIONS

The drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

### WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long term use of the drugs but has been observed following repeated short term courses. Enamel hypoplasia has also been reported.

TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST-EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of potential hazard to the fetus.

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

### PRECAUTIONS

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

Laboratory tests: In venereal disease when coexistent syphilis is suspected, dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

In long term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.

Drug interactions: Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin.

For concomitant therapy with antacids or iron-containing preparations and food see DOSAGE AND ADMINISTRATION section.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies are currently being conducted to determine whether tetracyclines have carcinogenic potential. Animal studies conducted in rats and mice have not provided conclusive evidence that tetracyclines may be carcinogenic or that they impair fertility. In two mammalian cell assays (L51784 mouse lymphoma and Chinese hamster lung cells *in vitro*), positive responses for mutagenicity occurred at concentrations of 50 and 10 mcg/mL, respectively. In humans, no association between tetracyclines and these effects have been made.

Pregnancy: Pregnancy Category D (see WARNINGS section).

Nursing mothers: Tetracyclines are present in the milk of lactating women who are taking a drug in this class. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the

drug, taking into account the importance of the drug to the mother (see WARNINGS section).

*Pediatric use:* See WARNINGS and DOSAGE AND ADMINISTRATION sections.

ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed (see DOSAGE AND ADMINISTRATION section).

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above (see WARNINGS section).

Renal toxicity: Rise in BUN has been reported and is apparently dose-related (see WARNINGS section).

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosus.

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported with tetracyclines.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function are known to occur.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose qd, as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For pediatric patients above eight years of age: The recommended dosage schedule for pediatric patients weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 3 mg/lb of body weight may be used. For pediatric patients over 100 pounds, the usual adult dose should be used.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice-a-day for 7 days.[2] As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose. The dose may be administered with food, including milk or carbonated beverage, as required.

Acute epididymo-orchitis caused by *N. gonorrhoeae:* 100 mg, by mouth, twice-a-day for at least 10 days.[2]

Primary and secondary syphilis: 300 mg a day in divided doses for at least 10 days.[2]

Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis:* 100 mg by mouth, twice-a-day for at least 7 days.[2]

Nongonococcal urethritis caused by *C. trachomatis* and *U. urealyticum:* 100 mg, by mouth, twice-a-day for at least 7 days.[2]

Acute epididymo-orchitis caused by *C. trachomatis:* 100 mg, by mouth, twice-a-day for at least 10 days.[2]

Inhalational anthrax (post-exposure):

ADULTS: 100 mg, of doxycycline, by mouth, twice-a day for 60 days.

CHILDREN: weighing less than 100 lb (45 kg); 1 mg/lb (2.2 mg/kg) of body weight, by mouth, twice a day for 60 days. Children weighing 100 lb or more should receive the adult dose.

The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

When used in streptococcal infections, therapy should be continued for 10 days.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration (see ADVERSE REACTIONS section).

If gastric irritation occurs, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

Concomitant therapy: Antacids containing aluminum, calcium or magnesium, sodium bicarbonate, and iron-containing preparations should not be given to patients taking oral tetracyclines.

Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

HOW SUPPLIED:

Doxycycline Hyclate Capsules are available as follows:

Equivalent to 75 mg Doxycycline
(opaque orange and green capsule) in:
Bottles of 50 capsules, NDC XX-XX imprinted Mutual XXX
Bottles of 500 capsules, NDC XX-XX imprinted Mutual XXX

Equivalent to 100 mg Doxycycline
(opaque yellow and light blue capsule) in:
Bottles of 50 capsules, NDC XX-XX imprinted Mutual XXX
Bottles of 500 capsules, NDC XX-XX imprinted Mutual XXX

Store at controlled room temperature 15°-30°C (59°-86°F).

DISPENSE IN TIGHT LIGHT-RESISTANT CONTAINER

REFERENCES

1. NCCLS Approved Standard:
M2-A3, Vol. 4, Performance Standards for Antimicrobial Disk Susceptibility Tests, Third Edition: available from the National Committee for Clinical Laboratory Standards, 771 East Lancaster Avenue, Villanova, Pa. 19085.
2. CDC Sexually Transmitted Diseases Treatment Guidelines 1982

Manufactured by:
MUTUAL PHARMACEUTICAL CO., INC.
Philadelphia, PA 19124 USA

Revised: XXX

**DORYX®** R
**(coated doxycycline hyclate pellets)**

## DESCRIPTION

DORYX® Capsules contain specially coated pellets of doxycycline hyclate for oral administration. Also contains lactose, NF; microcrystalline cellulose, NF; povidone, USP. The capsule shell and/or band contains FD and C blue No. 1; FD and C yellow No. 6; D and C yellow No. 10; gelatin, NF; silicon dioxide; sodium lauryl sulfate, NF; titanium dioxide, USP. Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline and available as doxycycline hyclate. The chemical designation of this light-yellow crystalline powder is alpha-6-desoxy-5-oxytetracycline. Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

## CLINICAL PHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile and excreted in the urine and feces at high concentrations and in a biologically active form.

Doxycycline is virtually completely absorbed after oral administration. Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/mL of doxycycline at 2 hours decreasing to 1.45 mcg/mL at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 mL/min). This percentage excretion may fall as low as 1–5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min). Studies have shown no significant difference in serum half-life of doxycycline (range 18–22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

**Microbiology:** Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative organisms. The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is common.

**Susceptibility Tests: Diffusion Techniques:** The use of antibiotic disc susceptibility test methods which measure zone diameter gives an accurate estimation of susceptibility of organisms to DORYX®. One such standard procedure[1] has been recommended for use with discs for testing antimicrobials. Doxycycline 30 mcg discs should be used for the determination of the susceptibility of organisms to doxycycline.

With this type of procedure, a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue and fluids (e.g., urine) in which high antibiotic levels are obtained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With the doxycycline disc, a zone of 16 mm or greater indicates susceptibility, zone sizes of 12 mm or less indicate resistance, and zone sizes of 13 to 15 mm indicate intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mcg tetracycline disc should give zone diameters between 19 and 28 mm for *S. aureus* ATCC 25923 and between 18 and 25 mm for *E. coli* ATCC 25922. The 30 mcg doxycycline disc should give zone diameters between 23 and 29 mm for *S. aureus* ATCC 25923, and between 18 and 24 mm for *E. coli* ATCC 25922.

**Dilution Techniques:** A bacterial isolate may be considered susceptible if the MIC (minimal inhibitory concentration) value for doxycycline is less than 4 mcg/mL. Organisms are considered resistant if the MIC is greater than 12.5 mcg/mL. MICs greater than 4.0 mcg/mL and less than 12.5 mcg/mL indicate intermediate susceptibility.

As with standard diffusion methods, dilution procedures require the use of laboratory control mechanisms. Standard doxycycline powder should give MIC values in the range of 0.25 mcg/mL and 1.0 mcg/mL for *S. aureus* ATCC 25923. For *E. coli* ATCC 25922 the MIC range should be between 1.0 mcg/mL and 4.0 mcg/mL.

## INDICATIONS AND USAGE

Doxycycline is indicated in infections caused by the following microorganisms:

Rickettsiae (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers).

*Mycoplasma pneumoniae* (PPLO, Eaton's agent).

Agents of psittacosis and ornithosis.

Agents of lymphogranuloma venereum and granuloma inguinale.

The spirochetal agent of relapsing fever (*Borrelia recurrentis*).

The following gram-negative microorganisms:

*Haemophilus ducreyi* (chancroid)
*Yersinia pestis* (formerly *Pasteurella pestis*)
*Francisella tularensis* (formerly *Pasteurella tularensis*)
*Bartonella bacilliformis*
*Bacteroides* species
*Vibrio cholerae* (formerly *Vibrio comma*)
*Campylobacter fetus* (formerly *Vibrio fetus*)
*Brucella* species (in conjunction with streptomycin)

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:

*Escherichia coli*
*Enterobacter aerogenes* (formerly *Aerobacter aerogenes*)
*Shigella* species
*Mima* species and *Herellea* species
*Haemophilus influenzae* (respiratory infections)
*Klebsiella* species (respiratory and urinary infections)

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriological testing indicates appropriate susceptibility to the drug:

*Streptococcus* species:

Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

*Diplococcus pneumoniae*.

*Staphylococcus aureus* (respiratory, skin and soft-tissue infections). Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to:

*Treponema pallidum* and *Treponema pertenue* (syphilis and yaws)
*Listeria monocytogenes*
*Clostridium* species
*Fusobacterium fusiforme* (Vincent's infection)
*Actinomyces* species

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

In severe acne, doxycycline may be useful adjunctive therapy.

Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis may be treated with oral doxycycline alone, or with a combination of topical agents.

Doxycycline is indicated for the treatment of uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis*.[2]

Doxycycline is inidicated for the treatment of nongonococcal urethritis caused by *Chlamydia trachomatis* and *Ureaplasma urealyticum* and for the treatment of acute epididymo-orchitis caused by *Chlamydia trachomatis*.[2]

Doxycycline is indicated for the treatment of uncomplicated gonococcal infections in adults (except for anorectal infections in men), the gonococcal arthritis-dermatitis syndrome and acute epididymo-orchitis caused by *N. gonorrhoeae*.[2]

## CONTRAINDICATIONS

The drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

## WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long term use of the drugs but has been observed following repeated short term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST-EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of potential hazard to the fetus.

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

## PRECAUTIONS

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

**Laboratory tests:** In venereal disease when coexistent syphilis is suspected, dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

In long term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.

**Drug interactions:** Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines in conjunction with penicillin.

For concomitant therapy with antacids or iron-containing preparations and food see DOSAGE AND ADMINISTRATION section.

**Carcinogenesis, mutagenesis, impairment of fertility:** Long-term studies are currently being conducted to determine whether tetracyclines have carcinogenic potential. Animal studies conducted in rats and mice have not provided conclusive evidence that tetracyclines may be carcinogenic or that they impair fertility. In two mammalian cell assays (L51784 mouse lymphoma and Chinese hamster lung cells *in vitro*), positive responses for mutagenicity occurred at concentrations of 60 and 10 mcg/mL, respectively. In humans, no association between tetracyclines and these effects have been made.

**Pregnancy:** Pregnancy Category D (see WARNINGS section).

**Nursing mothers:** Tetracyclines are present in the milk of lactating women who are taking a drug in this class. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the

drug, taking into account the importance of the drug to the mother (see WARNINGS section).

**Pediatric use:** See WARNINGS and DOSAGE AND ADMINISTRATION sections.

## ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines:

*Gastrointestinal:* Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed (see DOSAGE AND ADMINISTRATION section).

*Skin:* Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above (see WARNINGS section).

*Renal toxicity:* Rise in BUN has been reported and is apparently dose-related (see WARNINGS section).

*Hypersensitivity reactions:* Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosus.

*Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.*

*Blood:* Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported with tetracyclines.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function are known to occur.

## DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

*Adults:* The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or, as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For pediatric patients above eight years of age: The recommended dosage schedule for pediatric patients weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 2 mg/lb of body weight may be used. For pediatric patients over 100 pounds, the usual adult dose should be used.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice-a-day for 7 days.[2] As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose. The dose may be administered with food, including milk or carbonated beverage, as required.

Acute epididymo-orchitis caused by *N. gonorrhoeae:* 100 mg, by mouth, twice-a-day for at least 10 days.[2]

Primary and secondary syphilis: 300 mg a day in divided doses for at least 10 days.[2]

Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis:* 100 mg by mouth, twice-a-day for at least 7 days.[2]

Nongonococcal urethritis caused by *C. trachomatis* and *U. urealyticum:* 100 mg, by mouth, twice-a-day for at least 7 days.[2]

Acute epididymo-orchitis caused by *C. trachomatis:* 100 mg, by mouth, twice-a-day for at least 10 days.[2]

Inhalational anthrax (post-exposure):

ADULTS: 100 mg, of doxycycline, by mouth, twice a day for 60 days.

CHILDREN: weighing less than 100 lb (45 kg): 1 mg/lb (2.2 mg/kg) of body weight, by mouth, twice a day for 60 days. Children weighing 100 lb or more should receive the adult dose.

The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

When used in streptococcal infections, therapy should be continued for 10 days.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration (see *ADVERSE REACTIONS* section).

If gastric irritation occurs, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

**Concomitant therapy:** Antacids containing aluminum, calcium or magnesium, sodium bicarbonate, and iron-containing preparations should not be given to patients taking oral tetracyclines.

Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

## HOW SUPPLIED

*100 mg DORYX® (coated doxycycline hyclate pellets)* Capsules have a dark yellow transparent body, with light blue opaque cap; the capsule bearing the inscription "DORYX" and "WC" in a circle, printed in white. Pellets are colored yellow. Each capsule contains specially coated pellets of doxycycline hyclate equivalent to 100 mg of doxycycline, supplied in:

Bottles of 50 capsules ..... N 0430-0838-19

75 mg DORYX® (coated doxycycline hyclate pellets) Capsules have an orange transparent body, with green opaque cap; the capsule bearing the inscription "DORYX" and "75 mg" in black. Pellets are colored yellow. Each capsule contains specially coated pellets of doxycycline hyclate equivalent to 75 mg of doxycycline, supplied in:

Bottles of 60 capsules ..... N 0430-0836-20

**STORAGE CONDITIONS**

**Store at controlled room temperature below 25°C (77°F).**

## REFERENCES


1. NCCLS Approved Standard: M2-A3, Vol. 4, Performance Standards for Antimicrobial Disk Susceptibility Tests, Third Edition: available from the National Committee for Clinical Laboratory Standards, 771 East Lancaster Avenue, Villanova, Pa. 19085
2. CDC Sexuality Transmitted Diseases Treatment Guidelines 1982


**Rx only**


Revised March 2002

Manufactured by

**Faulding Pharmaceutical/DBL**

A Division of F.H. Faulding & Co. Limited

1538 Main North Road,

Salisbury, South Australia 5108

Distributed by

**Warner Chilcott, Inc.**

Rockaway, NJ 07866